DISCUSSION OF THE AMENDMENTS

Claim 1 is amended by including the heteroatoms on the cycloaliphatic radical and the substituents on the cycloaliphatic, aliphatic, heterocyclic and aromatic groups. Basis for these amendments can be found on paragraphs [0040], [0039], [0038], [0042] and [0045, 0047], of the published application US2007/0185158 (from pages 9 to 11 of the application).

Claim 2 is amended by indicating the substituents on radical R^1. support is found in paragraph [0039] (page 9, second paragraph, of the application).

Claims 3 and 4 are amended by specifying the substituents on the alkyl, alkenyl and alkynyl groups of radicals R^2-R^7. Support can be found in paragraph [0038] (page 9, first paragraph, of the application).

Claim 5 is amended by including the substituents on radicals R^8 and R^9. Support for this amendment can be found in paragraph [0038] and [0042] (page 9, first and last paragraph, of the application).

Claim 7 is amended.

Claim 8 is amended by indicating the possible substituents on radicals on aliphatic and aromatic groups. Support is found in paragraphs [0038] and [0045, 0047] (page 9, first paragraph, page 10, last paragraph, and page 11, second paragraph, of the application).

Claims 9, 10 and 11 are amended by specifying the possible substituents on the aliphatic groups of radicals R^2-R^9. Support is found on paragraph [0038] (page 9, first paragraph, of the application).

Claim 12 is amended.

Claim 13 is amended.

Claims 14-16, 18-44 and 46-72 are canceled.

Multiple dependencies are removed from claims 3, 4, 5, 7 and 17 which are now dependent only on claim 1.

Multiple dependencies are removed from claims 10, 11, 12, 13 and 45 which now depend just on claim 8.

The term "solvate" is deleted from claims 1, 8 and 13.

No new matter has been added by the submission of these amended claims

REMARKS/ARGUMENTS

Claims 1-17 and 45 are active.

Claims 14-16 stand withdrawn but are retained for the Office's consideration of rejoinder.

Non-elected claims 18-44 and 46-72 have been cancelled. Multiple dependencies have been removed.

RESTRCITION

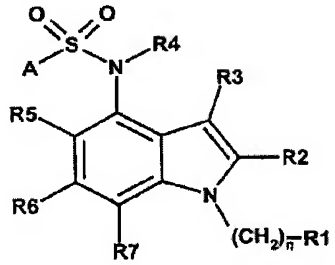
The objection to claims 1-13, 17, 18, 45 and 46 as containing non-elected subject-matter is respectfully traversed.

A lack of unity *a posteriori* objection was raised against the claims of the instant patent specification in view of document EP 0 815 861.

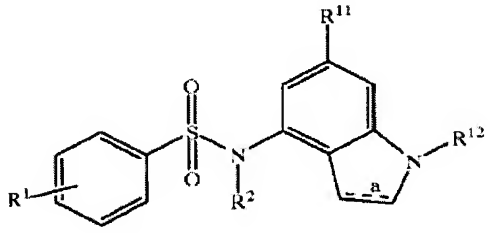
As stated in the Office Action, the Examiner considers that the special technical feature in the claims does not provide a contribution over the prior art. According to the Examiner, the special technical feature does not include the variables of the general formula, since the each variable has its own extensive definition. Therefore, Examiner requires limiting A radical to an optionally at least mono-substituted phenyl or naphthyl ring.

Applicant respectfully disagrees with said objection.

The subject-matter of the claims of the present patent application relates to a group of inventions so linked as to form a single general inventive concept within the meaning of R. 13.1 PCT since the subject-matter of the claims is defined in terms of alternative chemical compounds (Ia) and (Ib) having a common activity, i.e. regulation of the 5-HT_6 receptor, and a common significant structural element shared by all of the alternatives, that is, the common 1-substituted indole-4-sulfonamide core



The Examiner considers that in view of the (indole-4-yl)benzenesulfonamide derivatives



disclosed in EP 0 815 861, compounds (Ia) and (Ib) of the instant patent specification lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art.

The compounds of the present invention differ from those disclosed in EP 0 815 861 in that the substituent at the 1-position of the indole ring is $-(CH_2)_n-R^1$ wherein R^1 is an amine ($-NR^8R^9$) while R^{12} in EP 0 815 861 is hydrogen or C_1-C_7 alkyl.

Applicant respectfully disagrees with the lack of unity objection, since instant compounds claims fulfill all criteria of the Administrative Instructions under the Patent Cooperation Treaty, Annex B, paragraph (f), for "*Markush practice*" to which the Examiner refers:

- (A) all compounds have a *common property or activity*, namely, the inhibition of the 5-HT_6 receptor, as disclosed through the 5-HT_6 receptor inhibition values shown in TABLE of the present patent application (please refer to paragraph [0240] of the publication document); and

- (B)(1) all compounds share a *common chemical structure which occupies a large portion of their structures* (i.e. a significant structural element), namely a 1-substituted indole-4-sulfonamide core, a large portion with respect to any possible substituents.

Finally, all compounds of the present claims also fulfill criterion (v) of paragraph (f) of the Annex, since they are novel over the prior art document EP 0 815 861. Said document does not anticipate any of the compounds of the instant patent application since it discloses indol-4-yl-benzensulfonamide compounds with a different substituent at the 1-position of the indole ring, therefore, general formulae disclosed in EP 0 815 861 and the instant patent application do not overlap. All claimed compounds of formula (Ia) and (Ib) differ from EP 0 851 861 in that the indole ring is substituted at the 1-position with a $-(CH_2)_n-R^1$ group.

In view of the above, Applicants respectfully submit that all the claimed compounds provide a contribution over the prior art.

In addition, Applicants respectfully disagree with the Examiner's view, that the special technical feature does not include the variables of the general formula. As mentioned above, all the compounds of the present invention are substituent at the 1-position of the indole ring by a $-(CH_2)_n-R^1$ group, wherein R^1 is an amine ($-NR^8R^9$); whereas the compounds of EP 0 815 861 are substituted at the 1-position of the indole ring by a R^{12} group, which is selected from hydrogen and C_1-C_7 alkyl. The fact that said moieties are drawn in the general formula or just indicated as a list of possible substituents is irrelevant. They are equally an essential

part of the claimed formula and common to all the claimed compounds. Therefore, they are necessaryly part of the special technical feature.

From all the foregoing it is respectfully submitted that all claimed alternatives are of a similar nature and therefore all product claims are considered unitary within the meaning of R. 13.2 PCT.

THE REJECTION UNDER 35 USC 112, 2ND ¶

The rejection of Claims 1-13, 17, 18, 45 and 46 under 35 USC 112, second paragraph in view of the term "substituted" is no longer applicable as the specific substituents indicated for each radical have been provided in the amended claims.

The rejection pertaining to Claims 1-13, 17, 18, 45 and 46 based on R^1 is no longer applicable as claims 1 and 8 have been amended to define R^1 more particularly as described on page 9 of the application).

The rejection pertaining to Claims 18 and 46 is no longer applicable as claims 18 and 46 are canceled.

Withdrawal of the rejection is requested.

THE REJECTIONS UNDER 35 USC 112, 1ST ¶

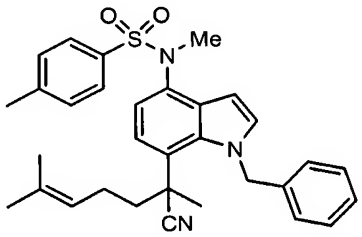
The rejection under 35 USC 112, first paragraph of claims 1-13, 17, 18, 45 and 46 pertaining to "solvate" is no longer applicable in view of the amendments removing this term. Withdrawal of the rejection is requested.

The rejection of Claims 18 and 46 under 35 USC 112, first paragraph is no longer applicable as claims 18 and 46 are canceled. Withdrawal of the rejection is requested.

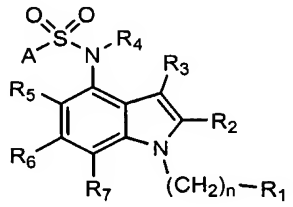
THE REJECTION UNDER 35 USC 102(b)

The rejection of claims 1-7 under 35 USC 102(b) citing Semmelheck et al. (*Tetrahedron Letter 1993, 34, 1399*) is respectfully traversed. That is, while Semmelheck teaches N-[7-(1-cyano-1,5-dimethyl-4-hexen-1-yl)-1-(phenylmethyl)-1H-indol-4-yl]-N,4-dimethyl-benzenesulfonamide (RN 148773-85-7), this compound does not fall within the scope of compounds defined in claims 1-7.

Notably, a comparison of the cited compound from Semmelheck and that defined in the claims is shown below:



RN 148773-85-7



(Ia) R_1 = -NR_8R_9 or cycloaliphatic radical

As defined in claim 1, R^1 may represent a -NR^8R^9 radical or a saturated or unsaturated cycloaliphatic radical. In contrast, the sulfonamide compound disclosed in Semmelheck et al. contains a phenyl group in the position corresponding to R^1 radical. According to IUPAC Compendium of Chemical Terminology (the "Gold Book"), aliphatic compounds are "*acyclic or cyclic, saturated or unsaturated carbon compounds excluding aromatic compounds*" (http://goldbook.iupac.org). In view of the above it is clear that phenyl is not a cycloaliphatic group, so compounds disclosed in Semmelheck et al. are not what is defined in the claims.

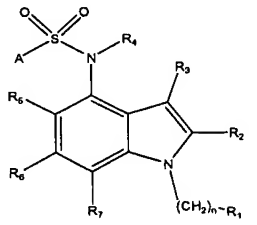
As claims 2-7 depend from claim 1 thereby having at least these same definitions, they are also not described by Semmelheck et al.

Withdrawal of the rejection is requested

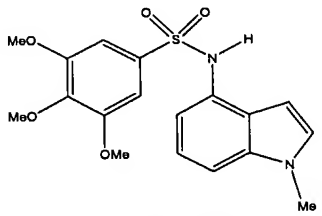
THE REJECTION UNDER 35 USC 103(a)

The rejection of claims 1-13, 17, 18, 45 and 46 under 35 USC 103(a) citing Li et al. (US 6521658) by the examiner. Applicants respectfully disagree.

Li et al. teaches compounds of formula (I) with compound 29C cited by the Examiner as structurally closest to the present invention. However, it is apparent that Example 29C is not a close structural homologue of compounds defined in the claims, see comparison below:



(Ia) R_1 = -NR_8R_9 or cycloaliphatic radical

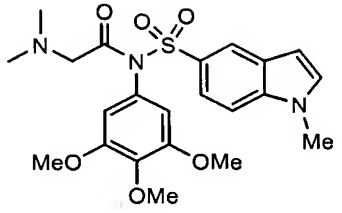


Example 29C

Therefore, Li's Example cited in the rejection is not an adjacent homolog that allows one to make the substitution as the Examiner has alleged. (See "Where an invention for which a patent is sought is a compound which is a member of an homologous series and the prior art discloses a *nonadjacent* member of that series, we do not consider the Hass and Henze cases authority for the legal presumption of obviousness of the claimed invention." *In re Elpern*, 326 F.2d. 762, 140 USPQ 224 (CCPA 1964)).

There is no teaching in Li that would have motivated one, faced with the problem of providing new inhibitors of the 5-HT_6 receptor (as the claimed compounds are), to modify the compounds of Li et al. arriving at the compounds defined in the claims. Nor is there a teaching in Li that would have provided any indication that modifying Li in the manner as suggested in the rejection to obtain compounds that are inhibitors of the 5-HT_6 receptor with a reasonable expectation of success.

Li et al. only discloses an extremely broad Markush formula, based on a phenyl ring, with multiple possibilities for substitution at the different positions. To arrive at the area of overlap with presently claimed compounds, the person skilled in the art would have to choose L^1 as $-NR^7SO_2-$ among the ten given possibilities, R^7 as hydrogen or aliphatic radical among sixteen options and R^1 as a heteroaryl group substituted with a cycloalkyl radical from a great number of alternatives. In addition, *Li et al.* does not provide any guidance to perform this specific election among the enormous amount of existing combinations. In this sense, none of the 108 examples included in this document overlaps with the general formula claimed in the present application. Even more, the preferred compound according to *Li et al.* (column 13, second paragraph), which is example 67 (reproduced below for reference), corresponds to an indol derivative which is bonded at position 5, instead of position 4, through the sulfur atom of the sulfonamide, instead of the nitrogen atom, wherein the sulfonamide nitrogen is substituted by a carbonyl group, instead of a hydrogen or aliphatic radical, and in which the indol nitrogen is bonded to a methyl group and not to a NR^8R^9 or a cycloaliphatic group. See *In re Elpern, Id.*



Example 67

Therefore, claims 1, 8 and their dependent claims cannot be obvious in view of what is taught by Li et al.

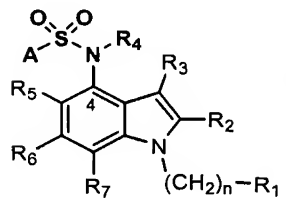
Withdrawal of the rejection is requeted.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

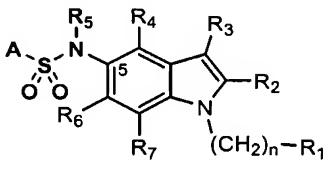
To the provisional and non-provisional-type double patenting rejection citing to US application 10/566,094 and patents US 7,414,070 and US 7,462,640.

With respect to the provisional rejection citing 10/566,094, in accordance with MPEP § 822.01, If the "provisional" double patenting rejection in the present application is the only rejection remaining, the examiner should then withdraw that rejection and permit the present application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the present application issues as a patent.

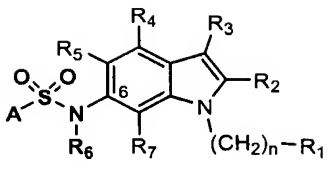
With respect to US 7,414,070 and US 7,462,640, The compounds disclosed in the cited patents correspond to positional isomers of the compounds of the invention, wherein the sulfonamide group is attached to different positions along the indol ring.



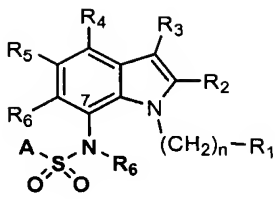
US 10/566,094



US 7,462,640



US 7,414,070



First, the applicant whishes to point out that no overlap exists between the present application and the subject-matter disclosed in any of these applications, since the claimed general formula in each case encompasses the corresponding stereoisomers but not positional isomers.

Positional isomers are compounds with the same molecular formula, i.e. the same number and kind of atoms, but different location of the functional groups along the chain or ring. As a consequence, they are different compounds with different three-dimensional shape, charge distribution and hydrogen bonding properties. These latter features are the ones that really determine the biological activity of a compound, and not the number and kind of atoms.

The sulfonamide moiety in these compounds is a highly voluminous group, compared to the planar indole ring, and as such it will notably contribute to the three-dimensional structure of the compound. As a consequence, a totally different steric situation can be envisaged for these four core structures, going from the compounds of the invention where the methylenic chain in position 1 and the sulfonamide group are completely opposed within the indole ring, to the compounds in US 7,414,070 where both groups are closely placed, creating a great steric congestion around those positions.

In addition, sulfonamide is not an electron-neutral radical, but rather contributes to the electronic properties of the compound. It is an electron-donating group with a lone pair on the nitrogen atom that increases the electron density of the aromatic ring through a magnetic resonance effect. Said resonance effect only allows electron density to be positioned at the

ortho- and para- positions of the ring in relation to the sulfonamide. Therefore, the charge distribution of the compound will be different depending on the position where the sulfonamide is located.

Moreover, this moiety contains several polar groups able to form hydrogen bonds, or other type of weak non-covalent interactions, with the active site of the receptor. This kind of bonding will only take place if the interacting groups are opposed. Obviously, displacement of the sulfonamide through the indole ring will determine whether said interactions can take place or not.

In summary, it is clear that the physicochemical properties of this class of compounds notably depend on the position of the sulfonamide moiety within the core structure. Therefore, the skilled person in search of compounds with similar properties would never modify the location of such group, as that would involve changes in the three-dimensional shape, charge distribution and hydrogen bonding properties, as shown above.

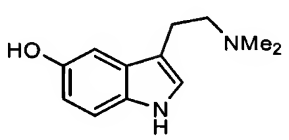
The active site of a receptor is usually a pocket with a concrete three-dimensional structure, which contains residues responsible for the specificity. This specificity is achieved through complementary shape, charge and hydrophilic/hydrophobic characteristics between the binding site of the receptor and the ligand. In other words, the primary concept behind receptor-ligand binding is that of complementarity, or 'fit' between ligand and active site. This matching depends on steric complementarity, i.e. the ligand must have a defined three-dimensional shape and size that fit well into the active site; and electrostatic complementarity, i.e. the presence of bonding interactions that attract and keep the two molecules together as a complex, which implies that hydrogen bond donors line up with acceptors, non-polar groups are opposite other non-polar groups and positive charges are opposite negative charges. Such

steric and electrostatic matching determines the ability of a compound to bind a receptor and, therefore, to stimulate the corresponding cellular effect.

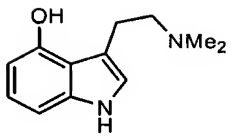
The skilled artisan, in search of new ligands for a given receptor, would not seek compounds with just the same number and type of atoms, but compounds wherein a similar affinity with the receptor could be expected, that is, compounds with analogous three-dimensional shape and electrostatic properties. That is not the case for the four above-mentioned core structures. In these structures, the sulfonamide group, which is essential for determining the steric and electrostatic properties of those compounds, is in a different position in each case, thus giving rise to compounds with significantly different properties. As a consequence, the skilled person would have never expected that the four core structures could be active as ligands for the same receptor, as the characteristics controlling the affinity receptor-ligand are different in each case. The fact that eventually the four classes of compounds were active as modulators for the same ligand is irrelevant, since that result was not expected *a priory* for the skilled person. It was a surprising and unexpected result.

The fact that positional isomers present different biological properties due to their different physicochemical properties, is illustrated below with several examples found in the literature.

For instance, bufotenin (compound A), wherein the hydroxyl group is in position 5 of the indole ring, is a poison that causes rise in blood pressure and paralyses the spinal and cerebral motor centres. In contrast, the positional isomer psilocin (compound B) is a psychoactive substance that increases excitability and causes hallucinations (*"The Chemistry of Heterocycles", 2nd ed., T. Eicher, S. Hauptmann, Wiley-VCH; p. 108*).

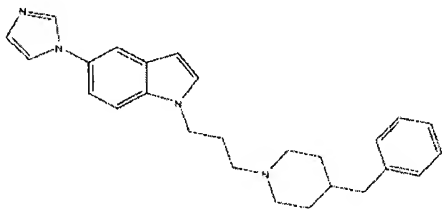


Compound A

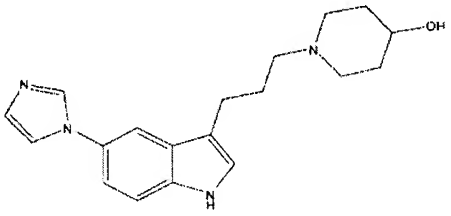


Compound B

In addition, compound (1) is claimed as inhibitor of thromboxane A2 synthesis in WO 9320065, while compound (2), having a similar substituent but in position 3, is described as highly selective h5-HT1D receptor agonist (Russell, M.G.; *J. Med. Chem.* 1999; 42(24); 4981-5001).

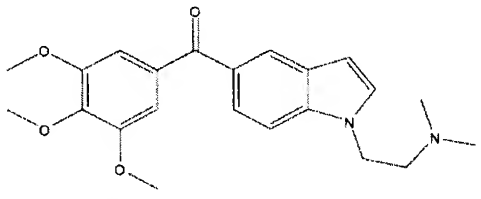


Compound (1)

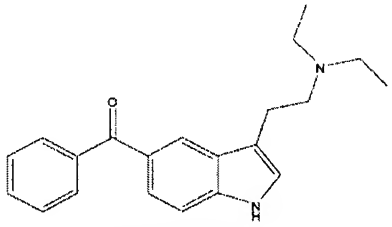


Compound (2)

A similar situation arises when comparing compound (5), which is described as potent antitubulin agent (Liou, J.P.; *J. Med. Chem.* 2007; 50(18); 4548-4552), with compound (6) (Leonard, B.E.; *Neuropharmacology* 1972; 11(3); 373-384), which is described as having effects on brain monoamines and their precursor amino acids.



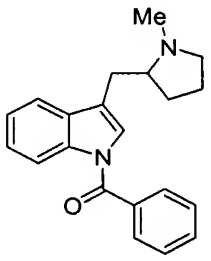
Compound (5)



Compound (6)

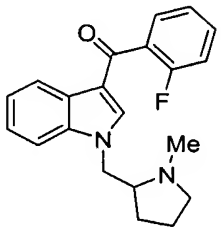
Last example refers to two different compounds that can be associated with a "positional isomerism" for which US patents have been granted: one of them proposed as 5-

HT_6 antagonist (US 6,100,291) and the other proposed for treating intraocular pressure or glaucoma (US 5,607,933), which are not related to 5-HT_6 receptor.



RN: 244122-12-1

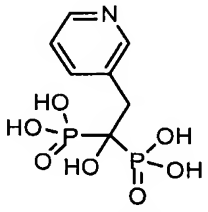
(US 6,100,291)



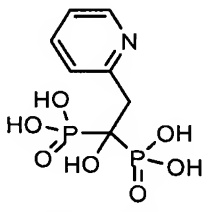
RN: 137642-51-4

(US 5,607,933)

See also *P&G v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 90 U.S.P.Q.2D (BNA) 1947 (Fed. Cir. 2009), finding the non-obviousness of 3-pyr EHDP (Actonel) over the positional isomer where the chain is connected to position 2 of the pyridine ring (2-pyr EHDP), instead of position 3.



3-pyr EHDP



2-pyr EHDP

Reconsideration and withdrawal of the rejection is requested.

A Notice of Allowance is requested.

Respectfully Submitted,

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